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ELEVATED INTERNATIONAL NORMALISED RATIO (INR) IS ASSOCIATED WITH AN INCREASED RISK OF
INTRAVENTRICULAR HAEMORRHAGE IN EXTREMELY PRETERM INFANTS

*Alessandra Glover Williams MD¹, *David Odd MD^{2,3}, Sarah Bates MD², Geoff Russell⁴, Axel Heep
MD^{2,3}

¹Royal United Hospital Bath, ²Southmead Neonatal Intensive Care Unit, ³School of Clinical Science,
University of Bristol, ⁴Department of Haematology, Southmead Hospital, North Bristol NHS Trust,
Bristol, UK.

*AGW and DO are equal first authors

Correspondence to

Axel Heep, MD, FRCPCH

School of Clinical Science, University of Bristol, Neonatal Intensive Care Unit,
Southmead Hospital, North Bristol NHS Trust, Southmead Road, Bristol, BS10 NB5, UK.

axel.heep@bristol.ac.uk

Phone: + 44117 4146800

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Abstract

The International Normalised Ratio (INR), a standardised method of reporting the prothrombin time, can be a surrogate marker of the vitamin K dependent coagulation pathways.

Objective: To evaluate the relationship between INR measurements in the first 48 hours of life, and subsequent development of Intra Ventricular Haemorrhage (IVH) in extremely preterm infants.

Methods: Single centre retrospective, observational cohort study of infants born at less than 28 weeks gestation. Main outcome measure was defined as the degree of IVH seen on cranial ultrasound examinations at day 7 postnatal age.

Results: 109/200 infants (mean gestational age 25.2 weeks (SD 1.27)) had coagulation results available. 26/109 developed IVH. Increased INR was associated with increased risk of a severe IVH OR 5.66 (1.56-20.59; $p=0.008$) and OR 6.50 (1.65-25.62; $p=0.008$) adjusted for gestation, birth weight and gender. INR was strongly associated with severe IVH in infants who did not receive blood products (OR 64.60 (1.35-3081.25)), $p=0.035$), but not in those who did (OR 2.93 (0.67-12.71), $p=0.151$)($p_{\text{interaction}}=0.086$).

Conclusion: An elevated INR in the first 48 hours of life may be useful to identify preterm infants at risk of severe IVH and may guide strategies to prevent the development, or limit the extension, of IVH.

Introduction:

Disruption of haemostasis in preterm neonates remains a significant concern because of the potential contribution to the development or extension of intra-ventricular haemorrhage (IVH) in extremely preterm infants [1]. The causative elements in the development of IVH are complex and inter-related but platelet and coagulation function remain an accepted element despite conflicting evidence [1-4]. We continue to examine this issue because IVH is a major predictor of the long-term neurodevelopmental outcome following extremely preterm birth [5].

Altered haemostasis has been a recognised issue within the care of preterm infants since 1957 [6].

Diminished levels of coagulation proteins have been reported in the fetal and neonatal population, [1, 7-10]. In addition to this immaturity of haemostasis, other factors that can often precipitate preterm delivery, such as placental dysfunction, Intra-Uterine Growth Restriction, or Foeto-maternal infection, are all likely to influence the haemostasis system directly [10-13]. In particular, co-existing perinatal inflammation has been demonstrated to adversely affect the Vitamin K dependent coagulation pathway (related to low concentrations of clotting factor VII) [10,11].

The understanding of the development of the coagulation profile in infants born extremely preterm, less than 28 weeks gestation is still incomplete. One of the challenges to research in this area has been the difficulty in establishing 'normative' data ranges for haematological parameters in extremely preterm infants, partly because extremely preterm birth is not a 'normative' state [10] and furthermore neonatal clotting studies are dependent on sample collection and regularly affected by activation of clotting during slow sampling [14].

Studies on coagulation profile in extremely preterm infants have either looked at individual coagulation factor levels [10,11,13,15,16] or coagulation profile measurements [17,18].

Several studies have looked at coagulation tests and subsequent development of IVH in neonates describing alterations in the Vitamin K dependent coagulation system and subsequent risk of IVH [1, 11,15,17-21]. A recent study supports the assumption that this association seems to be influenced by genetic variants in genes linked to Vitamin K dependent coagulation [22].

From the clinical point of view it seems crucial to provide a measure estimating the Vitamin K-dependent coagulation system in infants following preterm delivery, focussing on potentially available haemostatic strategies for treatment and prevention of IVH [23].

Currently it is not common practice in UK neonatal units to measure individual coagulation factor levels at routine lab testing within the first days of life [24]. First line coagulation profile measurements would usually include PT (Prothrombin Time), APTT (Activated Partial Thromboplastin Time) and Fibrinogen [12]. The assessment of INR would be of particular interest, as it presents a standardised method of reporting the PT. INR was devised to overcome inter-laboratory variability due to thromboplastin sensitivity during PT testing. INR is calculated: patient PT/control PT to the power of the international sensitivity index (ISI) [25]. INR and PT have been shown to be indicative of the Vitamin K dependant “extrinsic” coagulation pathway in neonates [7]. The association between INR values and development of IVH has been reported in a cohort of extremely preterm infants [18] supporting the assumption that INR could play a role in the understanding of the causative relation of prothrombin related haemostasis to risk of IVH.

The primary aim of this work was therefore to investigate the association between coagulation measures in preterm infants and the risk of developing IVH and secondarily to evaluate the influence of early blood product administration on any association.

Materials and Methods

Population: All infants born at less than 28 completed weeks gestational age and admitted within 48 hours of birth to Southmead Hospital, Bristol, UK, tertiary neonatal intensive care unit, between March 2008 and January 2012, were eligible for this study (n=218). Infants were excluded if they did not have ultrasound data recorded (n=18) or had no coagulation studies performed in the first 48 hours of life (n=91), leaving 109 infants for the main analysis (N.B. Not all infants had all measures of coagulation recorded and so denominators vary).

Exposure measures: All coagulation studies were performed as part of the routine admission blood sampling and analysed using the Sysmex CS-2100 analyser (Sysmex UK Ltd, Milton Keynes, UK).

Quality control of the coagulation testing was performed using Siemens Actin FS for APTT (n=479; mean 26.18 sec (SD 0.85 sec)), Siemens Innovin for PT (n=494; mean 11.18 sec. (SD 0.43 sec.)) and Siemens Thrombin for fibrinogen (n= 214; mean 2.57 mg/dl (SD 0.11 mg/dl)), (Siemens, Erlangen, Germany) [26]. Haematocrit (HCT), total white cell count (WBC), total platelet count were analysed using Sysmex XE-2100 analyser (Sysmex UK Ltd, Milton Keynes, UK). INR was calculated using a reagent with mean normal PT and international sensitivity index derived from internationally calibrated reference pooled adult plasmas. The reference range of the INR test for non-coagulated patients (whole blood, citrate tube) was 1.0-1.3. Where infants had multiple samples, the first recorded sample taken after admission to the unit was used. Infants were only included in the analysis if they had coagulation parameters measured within the first 48 hours of life. According to the unit protocol all preterm infants received Vitamin K (0.4mg/kg intramuscular) on admission to the neonatal intensive care unit [27]. Therefore, all of the coagulation parameter measurements were taken after administration of Vitamin K.

Outcome measures: Cranial Ultrasound Imaging was performed with a Philips HD11XE US machine (Philips, Guildford, UK) using a 8.5 MHz sector transducer. The presence of IVH was noted and

classified according to Volpe [28] at 7 days of age. All images were independently reviewed and categorised by one of the researchers (AH).

Demographics and covariates: Antenatal and perinatal characteristics of the study population were collected from patient electronic and written medical records. A full course of antenatal steroid treatment was defined as administration of two doses of 12mg betamethasone more than 24 hours prior to delivery. Data was collected regarding the frequency of administration of blood products (including packed red cells (PRC), platelets, cryoprecipitate and fresh frozen plasma) in the first 48 hours of life. Administration of blood products followed the local unit protocol.

Data analysis:

Initially patient characteristics were derived and then a comparison of demographics between those infants who had coagulation parameters measured in the first 48 hours, and those who did not was performed.

The association between coagulation results and gestation was investigated, as was the effect of being Small for Gestational Age (SGA birth weight below the 9th centile for gestation). The proportion of infants with IVH was calculated and the univariable association between coagulation measures and risk of IVH derived. Finally a logistic regression model was developed assessing the association between coagulation measures (as a continuous variable) and severe IVH (grade 3-4[28]). This was assessed unadjusted and adjusted for gestational age, birth weight and gender; clinical chorioamnionitis and initial CRP value. In sensitivity analysis the possible effect of blood products on this association was then tested using an interactive term.

The data did not follow a normal distribution so comparisons were performed using t-test, Chi-square or Mann-Whitney U as appropriate. All analyses were conducted with Stata 10 software (Stata Corp, College Station, TX), and results are presented as number (percent), mean (SD), or median (inter-quartile range) as appropriate.

Ethical approval for all data collection was obtained from the North West NRES committee, UK

(Reference: 12/NW/0903).

Results

Demographic information on eligible infants with cranial ultrasound results is given in **Table 1**, split by those with, or without coagulation measures (n=200); 91 infants did not have coagulation studies reported within the first 48 hours of life. When compared to the infants who did have coagulation studies available, these infants did not differ in major perinatal characteristics except a lower incidence of severe IVH (23.8% versus 7.7%; $p=0.008$) and a higher incidence of complete antenatal steroids (52.8% versus 72.2%; $p=0.005$). In particular there was no significant difference between the groups with respect to the CRIB score, reflecting no significant difference in risk of early perinatal morbidity [29].

Infants of lower gestations had higher fibrinogen ($p=0.004$) and platelet values ($p=0.027$), and some evidence of higher white blood cell counts ($p=0.051$), but there was little evidence of an association between with gestational age and INR ($p=0.439$) or HCT ($p=0.451$) measures (**Table 2**). SGA infants had lower fibrinogen levels (0.7mg/dL vs 1.8mg/dL; $p=0.0007$) but similar INR ($p=0.232$) and APTT levels to well grown infants ($p=0.496$). In total 60 (55%) of infants had no evidence of IVH demonstrated on the day 7 cranial ultrasound, while 26 (23.9%) had evidence of severe IVH (grade 3-4). There was little evidence of an association between fibrinogen and APTT plasma levels and the grade of IVH (Table 3). However increased INR was associated with an increase in the risk of IVH ($p_{\text{trend}}=0.003$).

Overall there was weak evidence that infants that received blood products had a higher risk of a severe IVH (21/26 (80.8%) vs 5/26 (19.2%), $p=0.069$), (**table 4**). Substitution of FFP and / or cryoprecipitate was associated with incidence of severe IVH (table 4). No significant difference was found for platelet substitution or PRBC transfusion and incidence of severe IVH in the study cohort.

The initial INR was not different for those who received blood products (1.5 (1.3-1.8)) or not (1.5(1.4-1.8); $p=0.358$). Initial fibrinogen concentration were significantly higher and initial platelets were significantly lower in infants receiving blood products (data presented in **table S1**).

In the logistic regression model an increased INR was associated with increased risk of a severe IVH in the unadjusted (OR 5.66 (1.56-20.59), $p=0.008$) and model adjusting for gestation, birth weight, gender, clinical chorioamnionitis and initial CRP (OR 5.994 (1.49-24.07), $p=0.012$), but little evidence for an association between APTT (adjusted OR 1.02 (1.00-1.04), $p=0.095$) or fibrinogen (adjusted OR 0.96 (0.69-1.33), $p=0.814$).

INR remained strongly associated with severe IVH in infants who did not receive blood products (OR 64.60 (1.35-3081.25)), $p=0.035$), but not in those who did (OR 2.93 (0.67-12.71), $p=0.151$) ($p_{\text{interaction}}=0.086$). Due to missing data for APTT and fibrinogen, all infants who had severe IVH with measures had received blood products so analysis of interaction was not possible for these measures.

Discussion:

We present a retrospective observational study examining coagulation parameters taken during the first 48 hours of life in a cohort of extremely preterm infants. Participants had a mean gestation of 25 weeks, and therefore a high risk of developing IVH; this is reflected in the incidence of severe IVH (23.9%) in the study population. We report an association between an elevated INR and subsequent development of IVH and some additional evidence that the delivery of blood products may reduce this risk. Although there is evidence that alterations in prothrombin related coagulation is associated with bleeding in newborn infants [11,17,18,20] this is, to the best of our knowledge, the first study to report this association in a cohort of this size and this degree of prematurity, or evidence that early delivery of blood products can reduce IVH risk.

The physiology of haemostasis during foetal development has been thought to change rapidly over each week of gestation [7,8] necessitating multiple sets of reference ranges. Many of the reference ranges for 'normal' data in extremely preterm infants are derived from measurements of coagulation proteins in foetal samples [7-9]. However, extremely preterm infants as reflected in our study cohort are likely to differ physiologically from foetuses in utero at the same gestation, because perinatal factors likely influence on the coagulation protein concentrations measured following preterm delivery [10,13]. This may result in clinicians seeing coagulation result figures outside any given reference range [17]. The challenge is to know at what level these abnormal results may increase the risk of IVH and adverse outcome in our patient population, and indeed what we may do to prevent or ameliorate this risk.

Previous studies have suggested that the lower the gestation, the more impaired the coagulation pathways [1,6,7,10,13]. However, our data did not confirm this correlation between impaired coagulation and shorter gestational age. It may be that our data differed from other studies, as coagulation studies were taken from our cohort of infants after the administration of Vitamin K, whereas others may have used data obtained prior to Vitamin K administration [10]. In line with

1 recent published data [17] our data did not support the assumption that coagulation is significantly
2 altered by 'being small for gestational age' as suggested earlier [13]. A previous study [18]
3 demonstrated a correlation between INR in the first 24 h of life and the occurrence of IVH in preterm
4 infants categorized by birth weight less 1500g. In this study, INR, PT and PTT values were significantly
5 associated to birth weight. In contrast to this finding, the association of INR and severe IVH in the
6 adjusted regression model in our study was not significantly influenced by either gestational age or
7 birth weight.
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10 Our study supports the assumption that INR in the assessment of prothrombin-related haemostatic
11 profile might be of relevance to the neonatal population. This is important for two reasons: firstly
12 the "extrinsic" coagulation pathway has been demonstrated to be particularly deficient in extremely
13 preterm infants [10,11], and secondly, this pathway seems to be particularly implicated in the
14 pathogenesis of IVH in preterm infants [20].
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18 The INR itself is calculated from the PT and PT measures time to fibrin clot formation in vitro, it is
19 therefore not a global measure of coagulation. As part of an initial assessment of coagulation in
20 preterm infants, the INR has inherent limitations because it is derived by comparison with a 'normal'
21 control value. Because of the difficulties defining normative data in extremely preterm infants, the
22 control value is derived from adult data, however the "normal" control value is a constant value in
23 relation to the PT as explained in the Materials and Methods section above [25]. As such, its
24 interpretation and clinical meaning can remain the same as if one were interpreting the PT.
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33 In the presented extremely preterm cohort, each increase in INR by 1.0 had an odds ratio of a severe
34 IVH of 5. This is, given the adverse neurodevelopmental outcome associated with severe IVH [28],
35 potentially a clinically important finding. This defect in the extrinsic pathway in preterm neonates
36 has been considered for potential for intervention to prevent IVH. One such example would be
37 antenatal administration of Vitamin K, much as we administer antenatal steroids to benefit the
38 foetus/neonate. Trials looking at the efficacy of such therapy were initially promising [15,31], but
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the Cochrane review on this topic concluded that 'Vitamin K administered to woman prior to very preterm birth has not been shown to significantly prevent peri-ventricular haemorrhage in preterm infants or to improve neurodevelopmental outcomes in childhood' [32].

We observed that there was some evidence that the early administration of blood products influenced the association between increased INR and increased risk of severe IVH. Although the relationship was only of weak statistical significance, it still may be a clinically important finding as a

15 risk attenuation with targeted blood product administration in prevention of IVH in extremely preterm born infants has not been described in the literature previously.

In addition to improving the concentrations of vitamin K dependent coagulation factors, which might prevent the initial occurrence of a haemorrhage, or limit its extension; we would suggest that the administration of blood products guided by functional echocardiography including assessment superior vena cava flow [33] (in our unit usually in a volume of 15-20 ml/kg,) provides colloid, increases intravascular volume, and contributes to haemodynamic stability at a very crucial time [3]. However, previous studies failed to demonstrate a benefit of prophylactic volume expansion, in particular using fresh frozen plasma concentrates on the incidence of IVH in preterm infants [34].

We were however limited by the retrospective study design, and the assessment of coagulation parameters may well have been subject to selection bias by the attending clinician at the time.

However, our data (Table 1) demonstrates no significant difference in most of the perinatal factors (including gestational age, birth weight, CRIB score, Apgar score, multiple delivery and mode of delivery) between the infants who had coagulation results available in the first 48 hours of life, and those that did not. The only significant finding was that those infants who had their coagulation parameters measured were less likely to have received a full course of antenatal steroids. Since antenatal steroids have been demonstrated to be protective against developing IVH [35], this, together with the degree of immaturity of our cohort, might have contributed to the comparably high proportion that had a severe IVH seen on day 7 Cranial US.

1 When considering the group of infants who received blood products for their abnormal coagulation,
2 this may have also been subject to selection bias based upon decisions made by the attending
3 clinician at the time. It is possible that the attending clinician would have been more likely to
4 administer blood products to those babies who were felt to be at higher risk of IVH. If this
5 hypothesis is true, then this would further strengthen our findings that administration of blood
6 products to extremely preterm infants with abnormal coagulation parameters in the 48 hours of life
7 may be associated with attenuation in the risk of development of severe IVH.
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10 The association between administration of coagulation factor concentrates [36,37] or fresh frozen
11 plasma [34, 38-40] and risk of severe IVH has been looked at previously, but may well warrant a
12 return of focus to this subject, both into the exact values at which coagulation abnormalities should
13 be acted upon in this group of extremely vulnerable infants, but also into which blood products
14 would be of most benefit in reducing IVH risk. The data presented add to the understanding on
15 coagulation in extremely preterm infants, hereby supporting the idea of a risk stratified coagulation
16 screening with focus on prothrombin dependent coagulation in a group of infants that are at
17 particularly high risk of IVH, aiming for prevention or limitation of the extension of an IVH.
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37 In summary, an elevated INR in the first 48 hours of life is associated with the development of IVH in
38 extremely preterm infants and this relationship may be attenuated by the early administration of
39 blood products. Future studies should focus on defining the exact coagulation parameter limits
40 where treatment should be offered, and which blood product may offer the most therapeutic
41 benefit to prevent IVH.
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Declaration of Interest statement

The authors report no declarations of interest.

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Table 1. Demographic data of the study population: Data split by availability of coagulation results.

Measure	Coagulation results available (n = 109)	Coagulation results not available (n = 91)	p value
Gestational age (weeks)	25.2 (1.27)	25.3 (1.14)	0.4218
Birth Weight (g)	775 (206)	787 (197)	0.6871
IVH grades 0/1/2/3/4; (n)	60/10/13/6/20	71/5/8/2/5	0.008
CRIB score*	12.1 (2.4)	11.5 (2.6)	0.2186
Apgar at 5 minutes	8 (6-9)	7 (7-9)	0.1140
Males	62 (56.9%)	48 (52.8%)	0.558
Born by SVD**	55 (50.9%)	41 (45.1%)	0.636
Multiple birth	31 (28.4%)	22 (24.2%)	0.496
A/N Steroids***	57 (52.8%)	65 (72.2%)	0.005

* CRIB
=
Clinical Risk Index for Babies Score [29], ** SVD = Spontaneous Vaginal Delivery, *** A/N Steroids = a Full course of antenatal steroids (see Methods).
Values are number (%), mean (SD) or median (IQR)

score

Table 2. Coagulation studies and full blood count in first 48 hours of life. Data split by completed week of gestational age.

Gestational Age in weeks; (n)*	Fibrinogen (mg/dl)	INR	PT	APTT (s)	Platelets (10 ⁹ /L)	HCT (%)	WBC (10 ⁹ /L)	IVH grades (0/I/II/III/IV)
23 (n=10)	3.6 (0.7-4.5)	1.6 (1.4-1.7)	16.1 (14.6-18)	60.1 (55.4-75.6)	182 (140-234)	0.42 (0.35-0.44)	8 (5.2-21.4)	4/2/1/0/4
24 (n=17)	1.8 (1.3-3.7)	1.5 (1.4-1.9)	14.9 (14.1-18.2)	52.2 (48.7-66)	182 (161-212)	0.42 (0.39-0.46)	7.6 (4.4-12.7)	9/2/5/3/6
25 (n=18)	2.9 (1.4-4.5)	1.5 (1.2-1.9)	15.5 (13.6-19.6)	49.3 (43.3-69.5)	222 (144-257)	0.38 (0.34-0.43)	10.3 (7.2-13.9)	15/1/5/0/4
26 (n=21)	1.1 (0.7-1.9)	1.6 (1.4-1.8)	16.4 (14.8-19.4)	52.4 (44.9-61.7)	147 (121-213)	0.43 (0.38-0.5)	5.6 (3.6-10)	20/3/0/1/3
27 (n=19)	1.2 (0.6-2.3)	1.5 (1.4-1.9)	16.7 (15-18.3)	59 (49.4-82.4)	165 (142-199)	0.43 (0.37-0.48)	5.8 (3.4-13.8)	12/2/2/2/3
P _{trend}	0.004	0.439	0.216	0.914	0.027	0.451	0.051	n.d.

Measures are given as median and inter-quartile range (IQR) ; * n= number of complete coagulation studies available for analysis.

Table 3: Coagulation parameters and diagnosis of IVH: Study population grouped according to grade of IVH on Day 7 cranial ultrasound [28]:

Grade of IVH	Fibrinogen (mg/dl) (n = 85)*	INR (n = 109)*	APTT (s) (n=91)*
0 (n=60)	1.4 (0.8-3.6)	1.5 (1.3-1.7)	52.4 (48.2-63.5)
I (n=10)	1.2 (0.7-1.8)	1.6 (1.3-1.8)	49.8 (43.3-58.6)
II (n=13)	2.4 (1.8-3.8)	1.6 (1.4-2.0)	54.9 (41.8-76.5)
III (n=6)	0.6 (0.5-4.8)	1.9 (1.7-2.3)	63.9 (52.0-89.3)
IV (n=20)	1.6 (1.1-4.1)	1.7 (1.4-1.9)	59.9 (50.4-73.6)
P _{trend}	0.959	0.003	0.109

Measures are given as median and inter-quartile range (IQR); * Number (n) of performed coagulation studies (fibrinogen, INR, APTT) performed are different according to availability of samples.

**Table 4: Substitution of blood products (no – bp; ffp, cryo, plts, prbc) and
diagnosis of severe IVH: Study population grouped according to grade of
IVH on Day 7 cranial ultrasound [28]:**

Blood product	Severe IVH Yes (n = 26)	Severe IVH No (n = 83)	p-value
any- blood product Yes/No; (n)	5/21	32/51	0.069
FFP Yes/No; (n)	15/11	13/70	0.0001
Cryoprecipitate Yes/No; (n)	1/25	1/82	0.381
ffp and/or cryo Yes/No; (n)	15/11	14/69	0.0001
Plts Yes/No; (n)	2/24	3/80	0.386
PRBC Yes/No; (n)	17/9	41/42	0.154